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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/786,362	06/25/2001	George M. Grass	109904-00028	6261

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EXAMINER	
LY, CHEYNE D	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 05/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/786,362	GRASS ET AL.	
	Examiner	Art Unit	
	Cheyne D. Ly	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *January 26, 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☒ Claim(s) *5* is/are objected to.

8)☒ Claim(s) *1-18* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 26, 2005 has been entered.

2. Claims 1-17, Specie A (gastrointestinal tract), are examined on the merits.

3. The prior rejections directed to Hale et al. (US 5,607,691 A), and Hale et al. (US 5,607,691 A) taken with Yang et al. (1994) in view of Jacobson et al. (US 5,773,423 A) have been withdrawn in response to the claim amendments.

OBJECTIONS

4. Claim 5 is objected to because having improper periods therein. It is noted that the use of internal periods such as "a." is improper because the MPEP states that each claim begins with a capital letter and ends with a period. Periods may not be used elsewhere in the claims except for abbreviations (See MPEP 608.01(m) [R-2]). Appropriate correction is required.

5. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

6. It is noted that page 1, lines 5-15, discloses related applications to the instant Application. However, the current status of the parent nonprovisional application(s) has not been included. For example, U.S. Application Serial No: 09/320,069 is just one of several application which has been abandoned. Applicant is required to update the status of each related non-provisional application listed in page 1, lines 5-15.

CLAIM REJECTIONS - 35 U.S.C. § 112, SECOND PARAGRAPH

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. Claim 1, lines 1-15, recites the "providing of primary library or portion thereof...generating in vitro bioavailability data...", however, the information generated from lines 1-15 are not needed in the steps recited in lines 16-20 which causes claim 1 to be vague and indefinite. It is noted that "test samples" recited in lines 16-20; there are not indication that the "test samples" in lines 16-20 are related to the "test samples" recited in lines 1-15. Further, line 16 of claim 1 recites "selecting a predetermined absorption profile" which is indicative of predetermination even before the claim practice starts. The metes and bounds of claim 1 is not clear because the relationship between the lines 1-15 and 16-20 as directed the data being utilized in the method. The same issue is present in claim 5. Clarification of the metes and bounds is required. Claims 2-4 and 6-17 are rejected for being dependent from claim 1 or 5.

10. Claim 7 recites the limitation "said transport mechanism data" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.

11. Claims 8 and 11 recite the limitation "said dissolution rate data" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim. It is noted that claim 6, line 9, recites "dissolution" however, claim 1 or 6 does not recite the determination of "dissolution rate data."

12. Claim 9, line 3, recites the limitation of "said compound library". The antecedent basis of said claim is not clear because claim 6 and 5 which claim 9 ultimately depends from recite "primary compound library" and "secondary compound library." Therefore, it is not clear whether the limitation of "said compound library" in claim 9 is directed to the "primary compound library" or "secondary compound library." The same issue is present in claims 10, 11, 13, and 14.

13. Claim 15 recites the limitation "said physiological model" in line 1. There is insufficient antecedent basis for this limitation in the claim. It is noted that claim 6, line 4, recites the limitation of "physiological segments" which is different from the limitation of "physiological model."

CLAIM REJECTIONS - 35 U.S.C. § 112, FIRST PARAGRAPH

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. NEW MATTER REJECTION.

16. Claim 1, line 16, recites the limitation of "selecting a predetermined absorption profile" which has been not been found in the instant specification as originally filed. It is noted that Applicant discloses the "in vivo absorption profile may be generated by any number of pharmacokinetic techniques" (page 16 and pages 42-43). However, the instant specification does not provide written description basis for the limitation of "selecting a predetermined absorption profile" in the amended claims. The same issue is present in claim 5, line 26.

17. Claim 1, lines 17-18, recites the limitation of "producing a secondary compound library...whose absorption profiles are better than or equivalent to the predetermined absorption profile" which has been not been found in the instant specification as originally filed. It is noted that Applicant discloses the production of secondary libraries (pages 23-24). However, the instant specification does not provide written description basis for a "secondary compound library" produced using the criteria recited in claim 1. The same issue is present in claim 5, lines 27-28.

Claim Rejections - 35 USC § 102

18. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

19. Claims 1-3, 5-10, 12, 13, 15, and 16 are rejected under 35 U.S.C. 102(a) as being clearly anticipated by Wessel et al. (Jul-Aug 1998).

20. Wessel et al. discloses the process of intestinal absorption (HIA) of drugs depends both on complex biological processes including passive membrane penetration (permeability), and on compound physicochemical properties including solubility, dissolution rate, and dissociation constants (page 732, column 1, lines 12-17). Wessel et al. discloses a method for predicting human intestinal absorption (HIA) for the design, optimization, and selection of candidates for the development of oral drugs. The method of Wessel et al. starts with a set of compounds with known %HIA values (page 726, column 1, Introduction section). The set of 86 drug and drug-like compounds and their experimentally derived %HIA values used the method of Wessel et al. were gathered from literature sources (page 727, column 1, Data Set section). Table 1, (page 728) cites reference 64 as one of the literature sources for the compounds and data utilized in the method of Wessel et al. It is noted that the Amidon et al. reference is not provided as prior art, but only to expand on the data source cited by Wessel et al. Amidon et al., as cited by Wessel et al., describes a method for estimating human oral drug absorption based on a simple tube model for drug absorption (*in vitro*). Using data generated from a perfused rat intestinal segment (*in*

vitro), Amidon et al. utilizes an equation for determining fraction dose absorbed (bioavailability) requiring the parameters of dose-to-solubility ratio and membrane permeability (Abstract etc. and Introduction section). It is noted that the description above is consistent with the definition of bioavailability (page 7) and "*in vitro* data" (page 18, line 10) disclosed in the instant specification, as in instant claims 1 and 5, lines 1-7.

21. The method of Wessel et al. is directed to *in vivo* animal models, cell membrane models such as Caco-2 cells, quantitative structure-property relationships, and chemical based assays (page 726, Introduction section, line 17, to column 2, line 10). Table 1 (page 728) cites the literature sources for the compounds. For example, reference 71 (page 733) describes the bioavailability of chlorothiazide from 50, 100, and 250 mg solution doses which represents the required limitation of "initial dose." The method of Wessel et al. therefore, derives a subset of 64 compounds with %HIA less than 100% HIA, and a subset of 22 compounds, with 100% HIA. The 86 compounds in the working data set were split into a training set of 76 compounds and an external prediction of 10 compounds (page 727, columns 1-2, Data Set section), as in instant claim 1, lines 8-20, and claim 5, lines 8-15 and 26-30.

22. The method of Wessel et al. is performed on a DEC 300 AXP Model 500 workstation utilizing HyperChem, CORINA and ADAPT software programs (page 727, column 1, lines 18-32) for generating the absorption profiles illustrated in Figures 1-3 (page 731), as in instant claim 2, and claim 5, lines 16-25.

23. The method of Wessel et al. therefore, derives a subset of 64 compounds with %HIA less than 100% HIA, and a subset of 22 compounds, with 100% HI, were selected. The 86 compounds in the working data set were split into a training set of 76 compounds and an external prediction of 10 compounds (page 727, columns 1-2, Data Set section). The type of descriptors (properties) include atomic weight, degree of lipophobic and lipophilic character, %HIA, and size which may be important to the ability of the drug to penetrate cell membranes (page 730, column 1, last two lines, to column 2, line 45), as in instant claims 3 and 16.

24. The method of Wessel et al. comprises multiple linear regression analysis for linking the property of interest to the structures via the descriptors (parameters). The multiple linear regression analysis is for determining the optimal subset of descriptors and the continuous reduction of the rms errors of %HIA estimation from subset to subset. The multiple linear regression analysis requires a genetic algorithm (page 729, column 1, Multiple Linear Regression Analysis section). In the Neural Network Analysis, the analysis comprises 6 descriptors and adjustable parameters (page 729, column 2, Neural Network Analysis section), as in instant claim 6.

25. It is noted that inclusion of a reference by Altenberg is not being used as prior art, but only to expand on the inherent characteristics of the "genetic algorithm" cited above. Altenberg describes the "genetic algorithm" as comprising differential equations (page 19).

26. The method of Wessel et al. is directed to *in vivo* animal models, cell membrane models such as Caco-2 cells, quantitative structure-property relationships, and chemical based assays

(page 726, Introduction section, line 17, to column 2, line 10). In addition to the libraries described in Table 1 (page 728), Wessel et al. utilizes MDL's Comprehensive Medicinal Chemistry database (page 727, 47-52) as in instant claims 7-10, and 13.

27. The method of Wessel et al. is directed to compounds solubility and stability in the gastrointestinal tract, absorption through the intestinal wall, and a low rate of first-class hepatic metabolism (page 726, column 1, lines 4-7), as in instant claims 12 and 15.

CONCLUSION

28. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547. The USPTO's official fax number is (571) 273-8300.

29. Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also

enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

30. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

31. Any inquiry concerning this communication or earlier communications from the examiner should be directed to C. Dune Ly, whose telephone number is (571) 272-0716. The examiner can normally be reached on Monday-Friday from 8 A.M. to 4 P.M.

32. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, Ph.D., can be reached on (571) 272-0718.

C. Dune Ly /CDL
5/2/05

Ardin H. Marschel 5/2/05
ARDIN H. MARSCHEL
PRIMARY EXAMINER